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| EXAMINER | |
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| SHUKLA,R | |
| ART UNIT | PAPER NUMBER |
| 1632 | 24 |

**DATE MAILED:** 10/25/01

**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner of Patents and Trademarks**

| Office Action Summary | Application No. 09/484,331 | Applicant(s) HARRINGTON ET AL. |
|---|---|---|
| | Examiner Ram Shukla | Art Unit 1632 |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED. (35 U.S.C. § 133)
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *23 August 2001*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *62-68* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *62-68* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *19*
4)☐ Interview Summary (PTO-413) Paper No(s). _____
5)☐ Notice of Informal Patent Application (PTO-152)
6)☒ Other *18*

## DETAILED ACTION

1. The response filed 8-13-01 has been entered.

2. Claims 62-68 are pending in the instant application.

### *Priority*

3. It is noted that the instant applications is a divisional application of SEQ ID NO 09/276,820 filed 3-26-1999, which is a CIP of 09/263814 filed which is a CIP of 09/253022 which is a CIP of 09/159643 filed 9-24-1998 which is a CIP of 08/941,223 filed 9-26-1997. It is noted that the first application in the series 52 pages, second application has 74 pages, third application has 118 pages, fourth application has 133 pages and the fifth application and the instant application have 154 pages of specification. From the specification, it can not be decided what part of the specification was added or deleted in each CIP because at the filing of each CIP the specification has been substantially altered and therefore, the priority date for the claimed invention of the instant application can not decided. Accordingly, the instantly claimed invention is assigned the priority of the filing date of 09/276820, that is 3-26-99. Applicants are advised to point to the parts of the specification that supports the claimed invention in each of the applications to claim priority to the listed parent applications.

4. **Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.**

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Specifically the application fails to comply with CFR 1.821(d), which states:

(d) Where the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing " in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO: " in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application.

It is noted that the instant application does not have any sequence listing in the specification nor a CFR has been submitted. Since, parent application 09/276,820 has a sequence listing, Applicants can request the transfer of the sequence information from 09/276,820 to the instant application. Furthermore, the specification discloses nucleotide and amino acid sequences in figures 14-16 and 29-35. However, these sequences are not identified by sequence identifiers. For compliance with sequence rules, it is necessary to include the sequence in the "Sequence Listing" and identify them with SEQ ID NO. It is noted that the parent application only lists 17 sequences in the sequence listing, however, the sequences of figures 14-16 refer to SEQ ID NO 18, 19, and 20. Accordingly, neither the parent application nor the instant application contains listing for these sequences. In general, any sequence that is disclosed and/or claimed as a sequence, i.e., as a string of particular bases or amino acids, and that otherwise meets the criteria of 37 CFR 1.821(a), must be set forth in the "Sequence Listing." (see MPEP 2422.03).

For the response to this office action to be complete, Applicants are required to comply with the Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

***Specification***

5. The abstract of the disclosure is objected to because it is too long. It is noted that the abstract is 26 lines long and more than 250 words. Correction is required. (See MPEP § 608.01(b)).

6. The disclosure is objected to because of the following informalities:

Text is missing in: lines 10 and 11 on page 130; line 22 on page 134 and line 30 on page 140.

Appropriate correction is required.

***Claim Rejections - 35 USC § 112***

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 62-68 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is referred to the revised interim guidelines on written description published January 5, 2001 in the Federal Register, Volume 66, Number 5, page 1099-111, (also available at www.uspto.gov).

When the claims are analyzed in light of the specification, instant invention encompasses a method of screening for compounds/drugs that interact with a gene product or that affect a desired phenotype of a cell and therefore, compounds would be an essential component of the screening method and that it would encompass any compounds, nucleic acids, proteins, organic compounds, etc. as conventionally recognized in the art. In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, the specification does not teach the structure of any compound or drug that would be used in the claimed method. It should be noted that the only description/reference to a drug in the specification is in lines 28-30 on page 11 continued in lines 1-2 on page 12. Next, then, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (i.e. other than nucleotide sequence), specific features and functional attributes that would distinguish different members of the claimed genus. In the instant case, the specification does not teach any characteristics of any drugs or compounds to be used in the claimed method. In fact, the

specification does not disclose any compounds that could be used in the claimed invention.

This limited information is not deemed sufficient to reasonably convey to one skilled in the art that Applicant is in possession of any drugs or compounds to be used in the claimed method at the time the application was filed. Thus it is concluded that the written description requirement is not satisfied for the claimed genus.

9. Claim 62-68 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

It is noted that the instant claimed method encompasses a method of drug discovery wherein an endogenous gene is activated when any vector is integrated

in the genome of a cell, however the specification as filed does not provide sufficient guidance as to how an artisan of skill would have practiced the claimed method and an artisan of skill would have required extensive experimentation to practice the claimed method and such experimentation would have been considered undue because the experimentation would not have been routine at the time of the invention as discussed below.

First, the issue is: if any vector is integrated into the genome of a cell, would it activate an endogenous or what is/are the required or essential components of a vector for practicing the claimed method. A vector, when broadly defined, is a sequence of genetic material used to introduce specific genes into the genome of an organism, for example, an expression vector etc. In the instant case, the integration of the vector in the genome of a cell has to cause activation of an endogenous gene, such that a gene product of the endogenous gene is produced in larger amounts than when the endogenous gene is not activated. It is conventional knowledge in the field of molecular biology and gene regulation of eukaryotic cells that activation of a gene can occur when the transcriptional regulation of the gene is modulated, for example, by replacing the endogenous promoter of the gene with another promoter which would be more active in a cell, or by introducing a sequence element, such as an enhancer in the close vicinity of the promoter of the endogenous gene such that the enhancer increases transcription from the promoter of the endogenous gene. Therefore, while a vector may integrate in a gene, it would not be able to activate the expression of the gene unless it has a promoter or an enhancer that would increase the expression of the gene. The specification on page 35, lines 3-6 discloses that a vector useful for the methods described in the instant application ideally may contain a transcriptional regulatory sequences that undergoes non-homologous recombination, however, there is no teaching in the specification as to how a vector that did not contain a transcriptional regulatory sequence would have been used in the claimed invention. As discussed above it was not routine in the art to activate an endogenous gene in a eukaryotic cell by integrating a vector that did not contain any transcriptional regulatory sequence and the specification also does not provide any guidance regarding this. It is noted

that while an artisan of skill would know molecular biology techniques, the artisan would not know as to what kind of vector that lacked a transcriptional regulatory sequence could be used in practicing the claimed method and therefore the experimentation required would be undue since there is no guidance in the specification or in the prior art.

Next, the issue is: what is drug screening or is the claimed method a method of drug screening? It is noted that a drug by conventional definition would be: any substance, other than food, used in the prevention, diagnosis, alleviation, treatment, or cure of disease (Merriam Webster's Collegiate Dictionary, 10th edition, page 355,1997). However, the steps of the claimed invention do not represent in any way represent a method of treatment, diagnosis, alleviation or prevention or cure of a disease and by practicing the claimed method an artisan of skill would not be able to determine whether a compound that was isolated by the claimed screening method would have any of the properties of a drug. The specification does not teach or contemplate as to how a compound isolated by the claimed method would be further processed or would have to go through other methods to determine its therapeutic value. It is noted that while methods of determining the therapeutic value or effects of a compound may be known in the prior art, an artisan would not know how to use a compound isolated by the instant method because there is not disclosure or teaching as to the relationship of a disease and a phenotype or symptom or disease to a compound being screened and because neither the specification nor the prior art teaches any guidance as to how to determine the therapeutic effect of a compound, an artisan of skill would have required undue experimentation to determine the therapeutic effects of a compound.

Next, the question is: can any compound be screened in the instant method or what compounds can be used in the instantly claimed method and as to how the compound screening would be carried out. It is noted that the specification, in terms of disclosing a method of screening for drugs, only provides a one sentence disclosure, "In highly preferred embodiments, the cells expressing the endogenous gene product are cultured under conditions favoring production of sufficient

amounts of gene product for commercial application, and especially for diagnostic, therapeutic, and drug discovery uses." It is emphasized that nowhere in the specification, all the steps of the claimed method of screening for drugs of claims 62 or 63 have been disclosed at one place. In fact, the steps d and e of the claim 62 and step d of claim 63 have not been disclosed in the specification and there is no guidance in the specification as to how these steps would have been practiced by an artisan. It is noted that the specification does not provide any guidance as to what is contemplated as the compound that could be used in the screening assay of the claimed invention in steps d and e of claims 62 and in step d of claim 63. It is noted that the prior arts, e.g. Truecheart et al (US 6,159,705, 12-12-00, effective filing date 9-24-1996) teaches a method of screening for pharmaceutically effective compounds that specifically interact with and modulate the activity of a cellular proteins, however, the method used in the prior art uses activation of an endogenous gene by homologous recombination or (see lines 62-67 in column 45 continued in lines 1-45). In fact the specification teaches away from a method wherein the expression of an endogenous gene is activated by homologous recombination (see page 6, lines 1-11 of the specification). Therefore, the method taught by the prior art can not be used for practicing the instantly claimed method. Furthermore, it is noted that in the method taught in the prior art, an artisan knows what gene was to be targeted and therefore, the artisan would has prior knowledge of the gene products of the endogenous gene activated and therefore would be able to perform steps d and e. However, in the instant case, an artisan does not have any knowledge what gene has been activated and therefore, step c is to be carried out to find a cell in which a desired gene has been activated. But it should be emphasized that even when a cell in which a desired gene is activated, there is no way of knowing if the desired phenotype observed in a selected cell is due to the activated expression of only the desired gene or due to a activation of multiple genes. In fact, the specification on page 32, lines 28-30, states that a single cell or different cells in a set of transfectants (library) can over express more than one protein following transfection with the same or different constructs. In such a case, an artisan would not be sure whether a compound isolated in step e was specific for

the desired gene or due to another gene, in other words, the method as recited would not yield identification of a compound that specifically activation a particular gene. In other words, the specification does not provide any guidance as to how to practice the claimed method. It is noted that while one could identify a cell wherein an endogenous cell was activated and there was an desired phenotype expressed by the cell, the specification does not provide any guidance as to what criteria would be used to select one or test compounds for use in the claimed method, what would be the structure of the compound or what would be the characteristics of the compound that would be used in the step d of the claimed method. Even if one had chosen a compound at randomly without any consideration, it is noted that an artisan had to use a step of comparing the phenotype of the treated cell with the phenotype of a non-treated cell and the specification does not describe any such step in the specification.

In summary, the specification, except for a reference to use of the claimed cell for potential therapeutic compound screening, there is not disclosure in the specification as to how the method of screening would be performed and therefore, an artisan would not have any guidance from the specification or in the prior art for practicing the claimed invention and would require extensive experimentation for determining as to how use any vector in activating endogenous gene expression, what compounds with what structure or characteristics to use in the claimed method, therapeutic efficacy of compounds, etc., as discussed above. It is noted that such experiments would not have been routine at the time of the invention and therefore, an artisan would have required undue experimentation to practice the claimed invention.

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 62-68 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 62 and 63 recite the limitation "said one or more cells" in line 1 of step c. There is insufficient antecedent basis for this limitation in the claim because step a recites the term "one or more eukaryotic cells" in line 1 and "said one or more cells" in line 2, whereas step b recites the term "said one or more cells" in line 1 and therefore, it is unclear as to whether the term "said one or more cells" in step c is referring to the term in step a line 1, line 2 or step b.

Claims 62 and 63 are vague and indefinite because it is unclear as to whether a desired gene recited in step c is the same as the activated gene recited in step b or whether it is a different gene.

Claim 62 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: a sub-step in step c wherein a desired phenotype in a cell in which a vector has been integrated is compared with the desired phenotype in another cell in which the vector has not been integrated and a step wherein the ability of a test compound to interact with a gene product of a desired a gene or effect of the compound on a desired phenotype is compared with those in another cell where the desired gene is not activated.

Claim 63 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: a sub-step in step c wherein the amount of a protein, encoded by a desired gene activated in a cell in which a vector is integrated, secreted in the cell culture medium is compared with the amount of protein in another cell in which the protein encoded by the activated gene is not secreted in the culture medium and a step wherein the ability of a test compound to interact with the secreted protein encoded by the desired gene is compared with that in another cell where the desired gene is not activated or the product encoded by the gene is not secreted..

***Claim Rejections - 35 USC § 102***

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

13. Claims 62 and 66 are rejected under 35 U.S.C. 102(e) as being anticipated by Truecheart et al (US 6,159,705, 12-12-00, effective filing date 9-24-1996).

It is noted that the claimed method encompasses a genus of a method of gene activation by integrating a vector in the genome of a cell, (i) by homologous and (ii) by non-homologous recombination, of which the specification discloses the method of non-homologous recombination, but is not enabling for the claimed invention, as discussed in the 112 first paragraph enablement rejection. The instant 102 e rejection is made to cover the method in which the endogenous gene is activated by homologous recombination.

Truecheart et al teaches recombinant yeast cells and an assay system for screening and identifying compounds that interact with and modulate the activity of a cellular protein, e.g., a receptor or an ion channel (see the abstract) and that the method allows for screening of a large number of compounds to identify compounds that induce or antagonize the bioactivity of a receptor (see lines 12-19 in column 8). This art further teaches that a test compound may be exogenously added and that the receptor protein is either endogenous (encoded by endogenous gene) or expressed by heterologous gene (see lines 25-29 in column 8 and lines 21-43 in column 10). The cited patent also teaches different terms, such as modulation, a compound (columns 10-12) and teaches the assay method wherein a test cell which includes a target receptor or ion channel protein whose activity is to be modulated and a that the ability of a compound to modulate signal transduction is scored by detecting up or down regulation of a detectable signal (column 13 and 14). Lines 63-67 in column 45 teaches that the endogenous promoter of a yeast cell can be

replaced, e.g., by homologous recombination, with a Bar1 promoter engineered to cause higher levels of expression of Bar1 upon pheromone stimulation. Therefore, Truecheart et al teaches a method of screening for compounds that alter the expression of an endogenous gene wherein the expression of the endogenous gene is activated by altering the endogenous promoter of the endogenous gene by homologous recombination. Accordingly, Truecheart et al anticipate the invention of claims 62 and 66.

***Response to Arguments***

Applicant's arguments with respect to claims 62-68 have been considered but are moot in view of the new ground(s) of rejection and new art applied. Regarding the 1.132 declaration by the inventor, it is noted that the statements made in the declaration are primarily targeted to the prior art by Treco et al (US 5,641,670) and because a new art has been applied; these statements would not be applicable to the instant rejection. It is noted that the instantly applied art for the instant 102e rejection teaches all the elements of the claimed invention of the claims 62 and 66. Regarding the issue of homologous recombination vs non-homologous recombination, even though applicants teach away from this method, as instantly claimed, the invention of claims 62 and 66 would encompass as a species the method wherein an endogenous gene is activated by homologous recombination.

14. No claim is allowed.

Applicants are advised to submit a clean version of each amended claim (without underlining and bracketing) according to **§** 1.121(c) and a copy of all the pending/under consideration claims. For instructions, Applicants are referred to http://www.uspto.gov/web/offices/dcom/olia/aipa/index.htm.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ram R. Shukla whose telephone number is (703) 305-1677. The examiner can normally be reached on Monday through Friday

from 7:30 am to 4:00 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda, can be reached on (703) 305-6608. The fax phone number for this Group is (703) 308-4242. Any inquiry of a general nature, formal matters or relating to the status of this application or proceeding should be directed to the Kay Pinkney whose telephone number is (703) 305-3553.

Ram R. Shukla, Ph.D.

RAM R. SHUKLA, PH.D
PATENT EXAMINER